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10/567,057	06/26/2006	Gert Daube	LEA 36807	4884

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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,057	DAUBE ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 4-5 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 07/13/2010 is acknowledged. Claim 1 was amended and claims 3 and 6-7 were cancelled. Claims under consideration in the instant action are claims 1 and 4-5.

Applicants' arguments, filed 01/14/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Rule 37 CFR 1.132 Declaration

Applicant's submission of the declaration of Dr. Bernd Stephan under 37 CFR 1.132 filed 07/13/2010 is acknowledged. The declaration is, however, not found to be persuasive in light of the reasons set forth below

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Instant Claim 1 recites “systemic treatment” in the preamble of the claim whereas the active step comprising administration is broader and not limited to just the systemic administration.

Response to arguments: Applicants argue that their amendment to the instant claim 1 overcomes this rejection. However, it is noted that the instant claim still has the specific "systemic treatment" in the preamble and the active step still comprises

administration which is broader and is not limited to just the systemic administration. As such the claims still recite a broad and narrow limitation and are as such indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

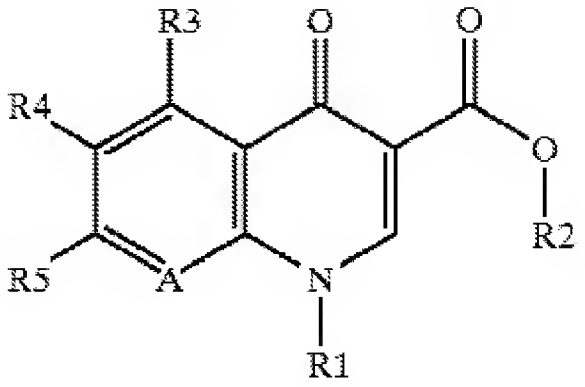
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1 and 4-5 under 35 U.S.C. 103(a) as being unpatentable over Schulz et al (WO 0145676, as translated by the US application US 2003/0045544, referenced in the IDS) in view of Vetter et al (US 5808076,) and Himmler et al (Abstracts of the interscience conference on Antimicrobial Agents and Chemotherapy (2002) is maintained for reasons of record restated below

Amendment to instant claim 1 incorporates the limitation of instant claim 3, which was previously rejected properly in the following original rejection. As such the amended claim 1 and claims 4-5 dependent on claim 1 are properly rejected by the original rejection set forth below.

Original rejection:

Schulz et al teaches the use of chemotherapeutic agents for the production of medicament useful for the topical and local treatment of diseases caused by bacteria in humans and animals (abstract). Schulz et al. teaches that in the oral region, tooth decay, inflammation of the eperiodontiumis both are caused by bacteria [0002-0003]. Schulz et al. teaches chemotherapeutic agents which are derivatives of quinolone-carboxylic acid or napthyridone carboxylic acid of general formula (I) shown below.



[0019] in which:

A	is CH, C-halogen, C—CH_3, C—CN, C—OCH_3, C—$OCHF_2$ or N,
R1	is C_1–C_5-alkyl, C_1–C_5-alkenyl, 2-fluoroethyl, cycloalkyl, bicycloalkyl, 2-fluorocyclopropyl, 1-oxetan-3-yl, methylamino, optionally substituted phenyl or pyridyl, or A and R1 together form the group C—O—CH_2—$CH(CH_3)$—,
R2	is hydrogen or C_1–C_3-alkyl optionally substituted by hydroxyl, halogen or amino,
R3	is hydrogen, halogen, methyl, amino or NH—NH_2,
R4	is hydrogen, halogen or amino, and
R5	is an optionally monosubstituted or polysubstituted mono-, bi- or tricyclic alicycle which is saturated or has at least one double bond and which optionally has at least one heteroatom in the ring system, or an aromatic mono-, bi- or tricycle optionally having at least one heteroatom,

Generic structure of formula (I) shown above by Schulz encompasses the instantly claimed compound pradofloxacin.

Schulz et al. teaches that these compositions when applied topically or locally have a beneficial action in the treatment of diseases caused by bacteria in the oral region of humans and animals [0023] particularly in topical treatment of pulpits due to caries disease and prophylaxis of dentin wounds treatment of infected root canal and other periodontal diseases [0036]. Accordingly, Schulz et al. provides an ordinarily skilled artisan to develop a method of treatment of oral cavity infections with pradofloxacin.

Schulz et al. does not teach the systemic administration of the drugs and does not specifically recite the name of the bacterial species which causes the oral cavity diseases as recited in instant claim 5 and 7.

However, Vetter et al. teaches preparation of orally administrable formulations of quinolone or natphyridonecarboxylic acids (abstract). Vetter et al. teaches the preferred quinolone compounds to include orbifloxacin, marbofloxacin, danofloxacin, difloxacin, ibafloxacin and danofloxacin (col.1, line 63 to col.2, line 1). Vetter et al. teaches that the formulations of the said fluoroquinolones are suitable for use in the fields of geriatrics and pediatrics or in veterinary practice in taste sensitive animals and that his formulations are active against several different bacterial species which includes bacterial species of "Actinobacillus and Bacteroides species" (col.4, lines 56 – 57) . Vetter teaches tablet formulations for systemic administration of the said fluoroquinolones (col.1, 27-30 and col.6, examples 2 and 3). Accordingly, Vetter et al provides motivation to an ordinarily skilled artisan to utilize the fluoroquinolones in oral tablet form for systemic administration.

Himmler teaches the synthesis of pradofloxacin and determination of its minimum inhibitory concentrations (MIC) in comparison with other fluoroquinolones such as difloxacin, enrofloxacin, marbofloxacin, orbifloxacin and sarafloxacin on strains of *E.coli*, *S. aureus* and *S. intermedius.* Himmler further teaches that of all the fluoroquinolones tested pradofloxacin had the lowest MIC for all the three strains of bacteria (E.coli and for *S.aureus* and *S. intermediius).* Himmler therefore provides motivation for an ordinarily skilled artisan to utilize pradofloxacin in lieu of other fluoroquinolones sited by Himmler as an effective antibacterial agent.

With regards to the specific bacterial species recited in instant claim 7, Schulz et al. teaches that the instantly claimed compound is highly effective in combating the bacteria of oral cavity when treated locally; Vetter teaches that fluoroquinolones such as orbifloxacin, marbofloxacin etc possess a broad spectrum of activity which includes the species of bacteria infecting the oral cavity such as bacteroides specie. As such upon systemic treatment pradofloxacin which is also a type of fluoroquinolones and is more effective than the other fluoroquinolones in in-vitro studies would elicit its activity by its antibacterial action against the bacteria in the oral cavity. " It is also noted that "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). As such the instantly claimed mechanistic functions of the compounds to treat the specifically recited bacteria would be present in the identical

compounds taught by Schulz et al and would therefore elicit these effects whenever it is administered .

In view of the foregoing references, the instantly claimed method for the systemic treatment of bacterial infections of the oral cavity with pradofloxacin would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Schulz et al teaches the use of fluoroquinolones such as pradofloxacin in topical and local treatment of oral cavity infections, Vetter teaches the systemic activity of fluoroquinolones against a very broad spectrum of bacteria which includes species of oral cavity bacteria and related species. Accordingly, an ordinarily skilled artisan would be motivated to combine the teachings of Schulz et al and Vetter et al to develop a method of treating bacterial infections of the oral cavity by systemic administration of pradofloxacin and other fluoroquinolones. Himmler provides additional motivation to an ordinary skilled artisan to utilize pradofloxacin as it showed the lowest MIC (minimum inhibitory concentration) in comparison to other fluoroquinolones in inhibiting *E.coli* and for *S.aureus* and *S. intermediius* . An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that such a method of treatment would provide alternative therapeutic options which has a broad spectrum of activity in treatment of oral cavity infections.

Response to applicant's arguments filed on :

Applicant traverses the above rejection with the following arguments:

a. Schultz et al. focuses the administration of the agents to topical or local administration.

b. Vetter et al. does not teach CN quinolones such as pradofloxacin and does not disclose the systemic treatment of bacterial infections of the oral cavity. Vetter et al. do not teach systemic treatment at all.

c. Infections taught by Himmler et al. do not comprise infections of the oral cavity.

d. Applicants argue unexpected results based on the data disclosed in the declaration submitted on 07/13/2010 and the instant specification.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

First, it should be noted that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims .Applicant is further reminded that the obviousness rejection is not an anticipation rejection. In obviousness rejection a combination of references is used, and the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the combination of the cited references. *In re Young*, 403 F.2d 754, 159 USPQ 725(CCPA 1968); *In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).*

Moreover, it is noted that rejections under 35 U.S.C. 103(a) are based on combinations of references, where the secondary references are cited to reconcile the

deficiencies of the primary reference with the knowledge generally available to one ordinary skill in the art to show that the differences between Applicant's invention and the prior art are such that they would have been modifications that were *prima facie* obvious to the skilled artisan. It is noted that the claimed invention is not required to be expressly suggested in its entirety by any one or all of the references cited under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Applicant has not overcome the rejection. Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

In response to applicant's arguments against each reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Schulz et al teaches the use of fluoroquinolones such as pradofloxacin in topical and local treatment of oral cavity infections, Vetter teaches the systemic activity of fluoroquinolones against a very broad spectrum of bacteria which includes species of oral cavity bacteria and related species. Accordingly, an ordinarily skilled artisan would be motivated to combine the teachings of Schulz et al and Vetter et al to develop a method of treating bacterial infections of the oral cavity by systemic administration of pradofloxacin and other fluoroquinolones. Himmler provides additional motivation to an ordinary skilled artisan to utilize pradofloxacin as it showed the lowest MIC (minimum

inhibitory concentration) in comparison to other fluoroquinolones in inhibiting E.coli and for *S.aureus* and *S. intermediius*

In response to applicant's argument against Schulz et al., while it is true that Schulz et al. only teaches topical and local administration, it still reads on the instant claims since in the instant claims the active step of the claim encompasses other routes of administration such as oral or topical as it does not specify the systemic treatment. Further, Schulze et al. provides clear motivation to an ordinarily skilled artisan to utilize Pradofloxacin for oral pathogen treatment.

In response to applicant's arguments against Vetter et al., examiner disagrees with the applicant that Vetter et al. dose not teach systemic administration at all. Vetter explicitly teaches oral administration of quinolone compounds in compositions such as tablets (see example 2, col.6 of the reference). Systemic therapy is defined as treatment that reaches cells throughout the body by travelling through the blood stream. Drugs administered orally, are distributed into the blood stream and are as such falls under the definition of Systemic administration. Besides, in the instant claims the active step of the claim encompasses other routes of administration such as oral or topical as it does not specify the systemic treatment. While the examiner agrees with the applicant's argument that Vetter et al. does not teach pradofloxacin, Vetter et al teaches several fluoroquinolones structurally similar to pradofloxacin (col.1, line 63 to col.2, line 1) and teaches that they are active against bacterial species which includes bacterial species of "Actinobacillus and Bacteroides species . This provides an ordinarily skilled artisan motivation to utilize oral/systemic treatment of fluoroquinolones to treat against these

specific bacteria and since pradofloxacin is also a fluoroquinolones as taught by Schulze et al, an ordinarily skilled artisan would be motivated to utilize pradofloxacin in the method of Vetter et al. and use systemic treatment of pradofloxacin in the method of Schulze et al.

In response to applicant's argument against Himmler, it is noted that Himmler reference is brought into the rejection for his teaching of the superior performance of pradofloxacin when compared to other fluoroquinolones, while the skilled artisan might not get to Himmler's reference for systemic treatment of bacterial infection of the oral cavity, an ordinarily skilled artisan would certainly look upon Himmler's references while evaluating the effects of pradofloxacin and would be motivated by the superior performance of pradofloxacin over other fluoroquinolones and would be motivated to utilize pradofloxacin instead of other fluoroquinolones in different applications.

In response to applicant's arguments of unexpected results, while the examiner has considered applicants data submission in the declaration and the data presented in the specification, the data is unpersuasive for the following reasons:

1. The data in the declaration is generated completely in the *in-vitro* setting and not under systemic conditions as instantly claimed. As it is well known in the art, conversion of data from the *in-vitro* studies to clinical setting involves evaluating several factors such as the pharmacokinetics, pharmacology, and pharmacodynamics and toxicity profile of the drug in the *in-vivo* methods. As such the *in-vitro* data presented does not provide the accurate "effective concentration" of pradofloxacin required to produce clinically effective results. Therefore while the date clearly demonstrates the

superior activity of pradofloxacin in comparison to des-cyano-pradofloxacin, the data is not commensurate to the scope of the claims.

2. With respect to the data in the instant specification, both Example A and example C (page 12) discloses *in-vitro* data. Example B (page 12) recites a clinical data which however, teaches the concentration of the pradofloxacin to be at 3 mg/kg and does not specify the mode of treatment (oral, systemic or topical) and while the specification recites that a significant reduction in periodontal pocket depth and in the total number of anaerobic bacteria was observed, no specific data is disclosed.

Accordingly, the unexpected results observed in these studies are with specific parameters and are not commensurate with the full scope of what is claimed and the data is not probative of nonobviousness of the full scope of the claims as discussed above.

As such, the arguments set forth by the applicant are unpersuasive and the rejection is maintained.

Conclusion

Claims 1 and 4-5 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614